REMARKS

Claims 78, 98-115, and 119-123, are pending in the present application. Claims 1-77, 79-97 and 116-118, have been previously canceled without prejudice or disclaimer.

Independent claim 78 is directed to "A method for changing the temperature of a biological matter from an initial temperature via an intermediate temperature to a final temperature, one of the initial and final temperatures being above the freezing point of said biological matter and the other being below the freezing point, comprising providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone, and changing the temperature of said sample by the following steps: (i) changing the temperature of the sample by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature." Claims 98-115 and 119 depend, either directly or indirectly, from claim 78.

Claim 121 is directed to "A method for changing the temperature of a biological matter from an initial temperature via an intermediate temperature to a final temperature, one of the initial and final temperatures being above the freezing point of said matter and the other being below the freezing point, comprising providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone, and changing the temperature of said sample by the following steps: (i) (a) changing the temperature of the sample by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature, said changing is achieved by moving the sample through a region with a temperature gradient from the initial temperature to the intermediate temperature, said sample has a leading end along the direction of movement; (b) moving the leading end of the into a region with a temperature gradient from the initial temperature to the intermediate temperature; (c) pausing the movement until seeding takes place at the leading end; and moving the sample through said region; (ii) further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature; and (iii) changing the temperature of said sample until the

majority of said sample is at the final temperature, said changing is achieved by moving the sample through a region with a temperature gradient from the intermediate temperature to the final temperature."

Claim 122 is directed to "A method for changing the temperature of a biological matter from an initial temperature via an intermediate temperature to a final temperature, one of the initial and final temperatures being above the freezing point of said matter and the other being below the freezing point, comprising providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone, and changing the temperature of said sample by the following steps: (i) changing the temperature of the sample by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) (a) further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature, said changing is performed by placing said sample in a region with the intermediate temperature, said region having a length along the direction of the movement of said sample and said length is not less the length of the sample along said direction of movement; (b) moving the

sample into the region with the intermediate temperature, until substantially the whole sample is within said region; (c) pausing the movement of the sample within said region until the temperature of the sample is substantially uniform throughout the sample and equals the intermediate temperature; (d) moving the sample out of said region; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature."

Claim 123 is directed to "A method for changing the temperature of a biological matter from an initial temperature via an intermediate temperature to a final temperature, one of the initial and final temperatures being above the freezing point of said matter and the other being below the freezing point, comprising providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone, and changing the temperature of said sample by the following steps: (i) changing the temperature of the sample by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature, and moving the

sample into a region with the intermediate temperature and subjecting the sample to the intermediate temperature in said region until the temperature of said sample in each cross-section taken perpendicularly to said direction reaches the intermediate temperature by the time it is moved out of said region; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature."

In support of the patentability of the presently pending claims, Applicant submits herewith two Declarations under 37 C.F.R. § 1.132 executed by Dr. Pasquale Patrizio ("the Patrizio Declaration"), Professor of Obstetrics and Gynecology at Yale University, Clinical Practice Director and Director of Yale University Fertility Center, and Amir Arav ("the Arav Declaration"), the inventor of U.S. Patent No. 5,873,254 ("the '254 patent") and a co-inventor of the instant application. In the Patrizio Declaration, Dr. Patrizio states that at the time of filing of the present application, it was generally known to those skilled in the art that freezing a biological sample without a cryoprotectant was possible. Annex A of the Declaration is Dr. Patrizio's *Curriculum Vitae*. In the Arav Declaration, Mr. Arav distinguishes the presently claimed subject matter from the subject matter in the cited art.

In view of the following, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, claims 78, 98-115 and 119-123 have been rejected under 35 USC § 112, first paragraph as failing to comply with the enablement requirement.

The Examiner asserts that the specification does not reasonably provide enablement for the freezing of semen from different species in the absence of

cryoprotectant.

Applicants respectfully traverse this rejection.

The test under 35 U.S.C. 112, first paragraph, for determining compliance with the written description requirement is whether the application clearly conveys that an Applicant has invented the subject matter which is claimed. *In re Barker*, 194 USPQ 470, 473 (CCPA 1977); MPEP 2163. Also, the Applicant must convey to the public what the applicant claims as the invention so that the public may ascertain if the patent applicant claims anything in common use or already known. MPEP § 2163. Lastly, the specification must convey that the applicant was in possession of the invention. MPEP § 2163. The Examiner is respectfully reminded that the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 191USPQ 90, 98 (CCPA 1976).

Applicants respectfully submit that the specification as originally filed fully complies with the written description requirement of 35 USC § 112, first paragraph. Specifically, Applicants submit that reading the present claims in view of the specification a skilled artisan would have sufficient description to make and use a method of freezing at least semen without inclusion of a cryoprotectant. As disclosed at page 12, lines 6-30 of the specification as originally filed,

> ...a method for double-freezing preservation of semen is provided comprising: (A) freezing the semen in one or more aliquots; (B) thawing at least one aliquot; (C) dividing said thawed aliquot to smaller aliquots; and (D) freezing at least one of said smaller aliquots.

Further, at page 13, lines 1-30 and page 14, lines 1-2 of the specification, an additional double-freezing method is provided that utilizes an isothermal-break method for the freezing or thawing of semen without the need for a cryoprotectant.

To further provide evidentiary support that the specification as originally filed fully complies with the written description requirement of 35 USC § 112, first paragraph, Applicants respectfully draw the Examiner's attention to the Patrizio Declaration, filed herewith as Exhibit A, wherein Dr. Patrizio, a Professor of Obstetrics and Gynecology at Yale University, Clinical Practice Director and Director of Yale University Fertility Center, declares that the present specification provides sufficient description for a skilled artisan to make and use a method of freezing at least semen without inclusion of a cryoprotectant. *See* the Patrizio Declaration. In particular, in paragraph 8 of the Patrizio Declaration, Dr. Patrizio declares that at the time of filing of the present application, it was generally known to those skilled in the art that freezing a biological sample without a cryoprotectant was possible. Applicants respectfully submit that the combination of this knowledge and the methods for double-freezing of semen without the need of a cryoprotectant disclosed, for example, at page 12, lines 6-30, page 13, lines 1-30 and page 14, lines 1-2, would enable a skilled artisan to freeze semen from different species without the need for a cryoprotectant.

In view of the foregoing, Applicants submit that claims 78, 98-115 and 119-123 fully comply with the written description requirement of 35 USC § 112, first paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

II. At page 2 of the Official Action, claims 78, and 98-115 and 119-123 have been rejected under 35 USC § 103 (a) as being unpatentable over US Patent No. 5,873,254.

The Examiner asserts that the '254 patent does not describe the size of the sample and that the generic description is not limited with regard to the size of the sample. Additionally, the Examiner asserts that the exemplification of the size of the sample in the cited reference is "ABOUT 1 cm x 1 cm x 0.5 cm," and that the "use of the term "about" in the above exemplification "permits a variation of undefined range around this measurement at the very least to ABOUT 2mm, which is the size of the container." Lastly, the Examiner asserts that mere scaling up of a prior art process is not sufficient to patentably distinguish over the cited references.

In view of the following, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of

ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Further, the Supreme Court in *KSR* reiterated the framework for determining obviousness that was stated in *Graham v. John Deere Co.* 383 U.S. 1, 148 USPQ 459 (1966). The four factual inquiries that were recited in *Graham* are as follows: (1) Determining the scope and contents of the prior art; (2) Ascertaining the differences between the prior art and the claims in issue; (3) Resolving the level of ordinary skill in the pertinent art; and (4) Evaluating evidence of secondary considerations, such as unexpected results. *Id.* As stated in **MPEP 2141**, secondary considerations such as unexpected results must be considered in every case in which they are present.

As described in **MPEP § 716.02(a)**, "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). *In Corkhill*, the claimed combination showed an additive result when a diminished result would have been

expected. This result was persuasive of nonobviousness even though the result was equal to that of one component alone. Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L-aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.). See **MPEP § 716.02(a) I**.

Presence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); *Ex parte Thumm*, 132 USPQ 66 (Bd. App. 1961) (Appellant showed that the claimed range of ethylene diamine was effective for the purpose of

producing "'regenerated cellulose consisting substantially entirely of skin'" whereas the prior art warned "this compound has 'practically no effect.' "). The submission of evidence that a new product possesses unexpected properties does not necessarily require a conclusion that the claimed invention is nonobvious. *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979). See the discussion of latent properties and additional advantages in **MPEP § 2145**. *See* **MPEP § 716.02(a) II**.

It is submitted that a proper case of *prima facie* obviousness has not been established because all the elements of the presently claimed subject matter are neither taught nor suggested by the cited references. However, assuming *arguendo*, all elements of the presently claimed subject matter are taught or suggested by the cited references, Applicants respectfully submit that a *prima facie* case of obviousness cannot be established in view of the data submitted herewith showing the unexpectedly superior results achieved with the presently claimed subject matter.

As discussed, claim 78 is directed to "A method for changing the temperature of a biological matter from an initial temperature via an intermediate temperature to a final temperature, one of the initial and final temperatures being above the freezing point of said biological matter and the other being below the freezing point, comprising ***providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters***, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone, and changing the

temperature of said sample by the following steps: (i) changing the temperature of the sample by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) ***further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature***; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature. (Emphasis Added). Claims 98-115 and 119 depend, either directly or indirectly, from claim 78.

Claim 121 is directed to "A method for changing the temperature of a biological matter from an initial temperature via an intermediate temperature to a final temperature, one of the initial and final temperatures being above the freezing point of said matter and the other being below the freezing point, comprising ***providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters***, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone, and changing the temperature of said sample by the following steps: (i) (a) changing the temperature of the sample by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the

outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature, said changing is achieved by moving the sample through a region with a temperature gradient from the initial temperature to the intermediate temperature, said sample has a leading end along the direction of movement; (b) moving the leading end of the into a region with a temperature gradient from the initial temperature to the intermediate temperature; (c) pausing the movement until seeding takes place at the leading end; and moving the sample through said region; (ii) ***further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature***; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature, said changing is achieved by moving the sample through a region with a temperature gradient from the intermediate temperature to the final temperature."

Claim 122 is directed to "A method for changing the temperature of a biological matter from an initial temperature via an intermediate temperature to a final temperature, one of the initial and final temperatures being above the freezing point of said matter and the other being below the freezing point, comprising ***providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters***, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone, and changing the

temperature of said sample by the following steps: (i) changing the temperature of the sample by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) (a) ***further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature***, said changing is performed by placing said sample in a region with the intermediate temperature, said region having a length along the direction of the movement of said sample and said length is not less the length of the sample along said direction of movement; (b) moving the sample into the region with the intermediate temperature, until substantially the whole sample is within said region; (c) pausing the movement of the sample within said region until the temperature of the sample is substantially uniform throughout the sample and equals the intermediate temperature; (d) moving the sample out of said region; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature."

Claim 123 is directed to "A method for changing the temperature of a biological matter from an initial temperature via an intermediate temperature to a final temperature, one of the initial and final temperatures being above the freezing point of said matter and the other being below the freezing point, comprising ***providing said biological matter in the form of a sample whose minimal dimension in each of two mutually***

perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone, and changing the temperature of said sample by the following steps: (i) changing the temperature of the sample by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) ***further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature***, and moving the sample into a region with the intermediate temperature and subjecting the sample to the intermediate temperature in said region until the temperature of said sample in each cross-section taken perpendicularly to said direction reaches the intermediate temperature by the time it is moved out of said region; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature."

Applicants respectfully submit that the presently claimed subject matter is directed to a method for the cryopreservation of relatively large semen samples. As described in the specification, the semen sample has a minimal dimension in each of two mutually perpendicular cross-sections exceeding 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone. *See* the present specification at page 6,

lines 6-13. The methods of the presently claimed subject matter describe changing the temperature of the semen sample from an initial temperature via an "intermediate" to a final temperature. The "intermediate" temperature is directly linked to the sample size, which has minimal dimensions in each of two mutually perpendicular cross-sections exceeding 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the outer zone changes more rapidly than the temperature of the inner zone.

In contrast the '254 patent describes a device and method of producing a uniform cooling rate of 0.1°C/minute throughout a biological sample. Further, the '254 patent describes methods for the freezing of semen involving cooling the semen sample from 30°C to an "intermediate temperature" slightly below the lipid phase transition temperature of the semen at a rate slow enough to prevent chilling injury, preferably about 1°C/minute. However, the '254 patent does not teach or suggest "***providing said biological matter in the form of a sample whose*** **minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters**." In particular, the '254 patent describes a sample size as being "about 1 cm x 1 cm x 0.5 mm," which is smaller than the sample size described by the presently claimed subject matter which has a "minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters."

Additionally, to further provide evidentiary support for the statements outlined in the previous Response, Applicants respectfully draw the Examiner's attention to the Declaration of Amir Arav, the inventor of the '254 patent and a co-inventor of the instant

application. In the Arav Declaration, Mr. Arav declares that the presently claimed subject matter is distinguishable from the subject matter described in the '254 patent. In particular at paragraph 6, Mr. Arav declares that the presently claimed sample size is significantly larger than the sample size described in the '254 patent.

In contrast to the presently claimed subject matter, Applicants submit that the '254 patent does not teach or suggest either ***providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone*** or ***further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature***. *See* claims 78 and 121-123.

However, assuming *arguendo,* that each of the elements were taught or suggested by the cited references, Applicants respectfully submit that the present methods provide unexpectedly improved cryopreservation of semen samples whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than the temperature in the inner zone. As discussed above, prior to the filing of the present application, it was within the knowledge of one of ordinary skill in the art that during cryopreservation the best

possible viability was obtained when the sample volume and size were relatively small and "ideal" temperature histories were maintained, as evidenced by the description in the '254 patent. In contrast, the presently claimed methods of the subject matter achieve unexpectedly superior results because successful cryopreservation was achieved with relatively large semen samples exhibiting different temperature histories during temperature change, for the outer portion and inner portion, whose minimal dimensions in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters. Also, Mr. Arav declares that prior to the filing date of the present application, persons having ordinary skill in the art of cryopreservation understood that in order to achieve the best possible viability results during the freezing process, the time spent at each temperature and cooling rates between temperatures, i.e., temperature histories, should be the same for each section of an entire biological sample. *See* the Arav Declaration at paragraphs 6 and 7. Accordingly, the results achieved by the presently claimed cryopreservation methods for the cryopreservation of relatively large semen samples that undergo different temperature histories, are unexpectedly superior over the methods described in the cited references.

In view of the foregoing, it is submitted that nothing in the '254 patent renders the presently claimed subject matter obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At pages 5 and 6 of the Official Action, claims 78, and 98-115 and 119-123 have been rejected under 35 USC § 103 (a) as being unpatentable over the '254 patent in combination with US Patent No. 4,131,200 (Rinfret) in light of Dayian et al.

The Examiner asserts that it would have been obvious to substitute the controlled freezing method of laterally varying thermal gradients, as described in the '254 patent, for the uncontrolled platelet freezing method described in Rinfret in light of the method for platelet cryopreservation described in Dayian et al.

In view of the following, this rejection is respectfully traversed.

A brief outline of relevant authority is set forth above and incorporated by reference herein.

As discussed above, the '254 patent does not teach or suggest either ***providing said biological matter in the form of a sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters, and at least one of the cross-sections having an outer zone and an inner zone such that the temperature of the sample in the outer zone changes quicker than that in the inner zone*** or ***further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature***. Accordingly, the '254 patent does not render the presently claimed subject matter obvious. Further, in view of the unexpectedly superior results obtained by the methods of the presently claimed subject matter, Applicants respectfully submit that the presently claimed subject matter is non-

obvious within the meaning of 35 U.S.C. § 103(a).

Rinfret do not remedy the deficiencies of the '254 patent. Rinfret patent describes a thermoplastic bag for the storage of isolated materials including blood platelets, and a method for long-term storage and utilization of such living cells including the introduction of same in the bag, *in situ* freezing and storage at cryogenic temperatures, and thawing and discharge from the bag. *See* Rinfret at column 1, lines 5-12.

In contrast to the presently claimed subject matter, Rinfret do not teach or suggest changing the temperature of the sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature. Accordingly, Applicants submit that Rinfret fails to teach or suggest all the elements of the presently claimed subject matter.

Dayian et al. do not remedy the deficiencies of the '254 patent and Rinfret. Dayian et al. describe a method for platelet cryopreservation which makes use of a glycerol-glucose mixture as the cryopreservative agent which permits the transfusion of the thawed

platelets without prior washing to remove the additive. *See* Dayian et al. at page 1, paragraph 2.

In contrast to the presently claimed subject matter, Dayian et al. do not teach or suggest changing the temperature of the sample whose minimal dimension in each of two mutually perpendicular cross-sections exceeds 0.5 centimeters by subjecting it to a temperature gradient from the initial temperature to the intermediate temperature until the temperature of the sample in at least one part of the outer zone equals the intermediate temperature whilst the temperature of the sample in the inner zone is different from said intermediate temperature; (ii) further changing the temperature of said sample by subjecting it to the intermediate temperature until the temperature of said sample in at least one cross-section is uniform and equals the intermediate temperature; and (iii) changing the temperature of said sample until the majority of said sample is at the final temperature. Accordingly, Applicants submit that Dayian et al. fail to teach or suggest all the elements of the presently claimed subject matter.

Applicants respectfully submit that a proper case of *prima facie* obviousness has not been established because all the elements of the presently claimed subject matter are neither taught nor suggested by the cited references. However, assuming *arguendo*, all elements of the presently claimed subject matter are taught or suggested by the cited references, Applicants respectfully reiterate that a *prima facie* case of obviousness would be rebutted in view of the unexpectedly superior results achieved with the methods of the presently claimed subject matter. For the sake of compact prosecution, the discussion

regarding unexpected results in section II above, is not repeated herein, but is incorporated herein by reference. For a detailed analysis, please *see* Section II of this response.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, none of the cited references render the presently claimed subject matter obvious within the meaning of 35 USC § 103 (a). Additionally, assuming *arguendo* that all of the elements were taught or suggested, the unexpected results presented herein rebut any prima facie case of obviousness. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

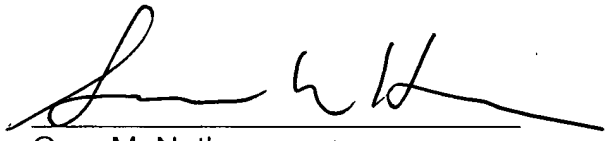
CONCLUSION

Applicants assert that the claims are in condition for immediate allowance and early notice to that effect is earnestly solicited. Should the Examiner deem that any further action by Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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THE NATH LAW GROUP
112 South West Street
Alexandria, Virginia 22314
Tel: (703) 548-6284
Fax: (703) 683-8396

Gary M. Nath
Registration No. 26,965
Susanne M. Hopkins
Registration No. 33,247
Ari G. Zytcer
Registration No. 57,474
Customer No. 20529